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Abstract

This paper explores the potential for simplicity to reveal new biological understanding. Borrowing selectively from physics thinking, and contrasting with Crick's reductionist philosophy, the author argues that greater emphasis on simplicity is necessary to advance biology and its applications.

Is it the destiny of biology that the cell is to be comprehensible at some later time only to supercomputers and the superorganism of 100 000 biologists, but not a single human mind? At face value the answer is a reluctant 'yes', based on the increasingly central role of the computer in biology, and the increasingly focussed expertise of even the most brilliant biologists.

Given the steady flow of public funds into biological research, this worrying destiny is not of concern to the daily cog-turning of the biological research machine. There is most certainly no shortage of detailed questions to ask nor talented and ambitious biologists to answer them. The purpose of this short piece, and the motivation of the author, is to step back from the machine for a moment and reflect on comprehensibility, viz. simplicity, of biology; in particular the cell, but by implication, multicellular organisms, and pathologies and populations thereof. To aid reflection, I have broken this essay into three sections, each supported by an equation of sorts, and, to keep the author on his toes, a stern warning from Francis Crick.

Evolution

Equation (1): physics does not equal biology

'Biologists must constantly keep in mind that what they see was not designed, but rather evolved' [1].

As a general rule, if one hears a physicist proclaim that biology, or actually any other subject, is simple, one needs to stand one's ground and fight (and the author states this as someone educated as a theoretical physicist). There is a naivety of some physicists'

outlook that can be charming from a distance, but becomes increasingly frustrating on closer approach. For example, for many years we have as a society been recipients of the theoretical physics mantra of the 'theory of everything', yet this has failed to deliver much insight beyond its own reductionist remit. That such bold proclamations did not ring true was noted many decades ago [2], and physics as a discipline continues to broaden its horizons, distancing itself from the idea that everything can be explained once we unify gravity and quantum mechanics.

Indeed, naïve applications of physics to biology will bounce off the monolithic unknowns of life without leaving much more than a scratch or two. The underlying principles of the physical universe can be encapsulated in a handful of differential equations (attributed to Newton, Maxwell, Schrödinger, *et al*). This, understandably, has given physicists a profound confidence that the Universe is comprehensible, quantifiable and predictive. Life, however, remains generally aloof from these underlying physical laws. I am not trying to revive the *élan vital*, but am simply stressing that the universality of physical laws does not have obvious explanatory power when applied to cells and the like. One could imagine writing down the Schrödinger equation for the cell, but it would be little more than an endless shopping list of myriad atomic interactions and completely intractable and therefore useless.

Crick's reminder to biologists of the fundamental importance of evolution in biology (echoing Dobzhansky's more elegant and well-known phraseology) is of even more pressing import to physicists. Life, as we know it on Earth, has emerged from billions of years of evolution. The ever-changing fitness landscapes that

have dictated the flow of natural selection are irretrievable, and we, as scientists in the twenty-first century, are like eager children on Christmas morn, presented with dazzlingly complex toys, which frustratingly have no instruction manuals (batteries are included though!). Evolution is a profound guiding principle, but not terribly utilitarian. Consequently the biology community has, perhaps inevitably, found traction and success in discovering, describing and understanding the molecular components of life and their interactions. What other approaches could or should we be taking? I will argue that physics can indeed help provide an answer to this question.

‘Small-minded’ fundamentalism

Equation (2): small does not imply fundamental and vice versa

‘Almost all aspects of life are engineered at the molecular level, and without understanding molecules we can only have a very sketchy understanding of life itself’ [1].

Crick instructs us to find the secrets of life in the molecules. Decades of such endeavour by hundreds of thousands of intelligent people have led to awe-inspiring molecular discovery and reams of information, but we still struggle with general principles and higher-level understanding of the cell and the organisms built thereof. How can we make the leap from molecular details to an over-arching comprehensible theory of life? Some inspiration and a partial answer may be found from complex physical systems that have been understood using higher-scale concepts.

Cells are complex and so, to a lesser degree, is water. We understand a lot about the properties of water. That understanding is for the most part independent of the molecular details of H₂O. At atmospheric pressure, water is a liquid between 0 °C and 100 °C. The liquid state is enigmatic—neither completely ordered like most solids, nor completely random like a gas. Molecules in a liquid stay in each other’s vicinity, but promiscuously change partners. At higher scales, the liquid flows, and forms droplets; it has eddies and can become turbulent. If one lowers the temperature of water, it will abruptly, at 0 °C, freeze into a solid we call ice (of which there are fifteen phases, depending on pressure). We have good theories for much of this, and these theories do not generally rely on molecules, and, on the whole, cannot even be derived from molecular details. The liquid state is an *emergent* property, as is the phase transition separating it from a crystalline solid. The flow of water, and the beautiful patterns that result, can be described by fluid mechanics, a branch of science that is highly successful and practical, and yet formulated without any reference to molecules. The same is true of the modern theory of phase transitions developed by Kenneth Wilson *et al* in the 1960s. These theories are as fundamental as any in science, and yet do not deal with small entities.

Many equivalent examples can be given, such as the emergent property of silicon, i.e. semiconductivity, which has been engineered to create information technology and has changed our world. Our understanding and theoretical grasp of semiconductors is based on solid-state physics; only a few details about the outer electrons of the silicon atom are required for the formulation of this branch of physics, which relies profoundly on a set of meta-atomic concepts, such as Bloch states and the Fermi surface.

Returning to water, in biological terms it has a ‘genotype’ three ‘nucleotides’ in length (H, O and H), and yet an almost infinite array of ‘phenotypes’. Our knowledge of the H₂O molecule itself is excruciatingly detailed, and yet almost impotent in providing understanding of water at higher scales. If molecular detail is mainly irrelevant to our understanding of water at the micron scale and above, why is it crucial, as Crick states, for understanding life at the micron scale and above, i.e. the cell and organisms comprised thereof? Is it all down to evolution, creating a profoundly different form of complexity?

To probe this question, consider a typical city, which is a system with complexity quite different to that of water. One might argue that some sort of evolution has been at work in selecting large human groupings (that we now call cities) of high fitness. Is the complexity of a city then perhaps more like that of a cell, where the understanding is to be found in the components? City ‘molecules’ could perhaps be machines, individual humans, and the like. Does understanding the myriad city components such as the automobile engine, the internal workings of a cash machine and the daily habits of an insurance agent provide understanding of a city? Or are higher-level concepts, such as transport, politics, employment, crime, healthcare and education, more helpful?

I would favour the latter set, whose essential role within the system is largely independent of the components, and yet whose properties and interactions are of profound consequence to the robustness and vitality of a city.

Is life unique? Is it a world apart from hydrodynamics and town planning?

The hindsight of simplicity

Equation (3): simple does not imply obvious

‘While Occam’s razor is a useful tool in the physical sciences, it can be a very dangerous implement in biology. It is thus very rash to use simplicity and elegance as a guide in biological research’ [1].

The best theories we have of Nature are simple. In fact, they are for the most part annoyingly simple, and one cannot imagine how we did not know those things prior to them being discovered. Simplicity is obvious with hindsight, but before discovery is not obvious by definition. Simple discoveries often encounter two

strong rebukes from the scientific community: ‘it is wrong’, followed after argument by ‘well, we all knew that’.

And yet, surely, simplicity must be our ultimate ambition in science. Simplicity is power. Simplicity in its purest form takes a small number of inputs and gives a large number of outputs. The inputs are generally assumptions and the outputs are generally new concepts and predictions. The higher the ratio of outputs to inputs, the better, and, more often, the simpler is the theory. Think Newton, Darwin, Maxwell, Einstein. Indeed, Einstein’s special theory of relativity must perhaps take first prize in the simplicity stakes: a theory defined by two rather benign postulates, which when logically pursued yields time dilatation and the equivalence of mass and energy, and changed the world. Darwin’s theory of natural selection, though expressed more verbosely in the original, is a close runner-up. Theories with an output/input ratio less than one should be discarded. Such theories have been described, delightfully, as ‘not even wrong’ (a remark attributed by Rudolf Peierls to Wolfgang Pauli).

Crick advises us that despite the undoubted power of simplicity in physics, one should park it at the door in biology. I profoundly disagree with this advice, though Crick’s warning resonates with me deeply. On reflection, I believe the dissonance is in Crick’s confounding simplicity with elegance. Crick quite rightly distrusted elegance in biology following the ineffectiveness of elegance in deciphering the genetic code. Elegance is a subjective aesthetic that physicists have found to be very useful in certain contexts, particularly high-energy physics, and is often related to the concept of symmetry. In other branches of physics, elegance is not a driver for discovery, yet simplicity is. I believe biology will benefit from a similarly nuanced position. One cannot imagine that elegance has played a fundamental role in evolution, while simplicity on the other hand is not too distant from concepts such as robustness and evolvability, and undoubtedly has much to offer in unlocking life’s secrets.

Reading this last paragraph through biology spectacles, I can see the objection that evolution has yielded mechanisms that are anything but simple, implying that simplicity was not a driver. One has only to think of the subtleties of eukaryotic transcription and translation, or the twists and turns of glucose metabolism. The key point I think is not to mistake the wood for the trees. The molecular decorations of fundamental processes are indeed complex, dazzlingly so. But simplicity should be sought at higher scales, drawing on our experience with water and solid-state physics.

To illustrate this point from another perspective, consider the remit of thermodynamics—to understand the phenomenon of heat. A complete theory of heat was developed between 1820 and 1860, most notably by Carnot, Kelvin, and Joule. None of these individuals used the existence of molecules upon which to base their ideas. Thermodynamics arose

from a combination of clever experiments and deep thought, and was encapsulated in a few laws, which are regarded to this day as fundamental pillars of science. Entirely new concepts were developed, such as thermodynamic temperature, entropy and free energy. If these individuals had had access to molecular ‘big data’ on gases, would this have helped or hindered them? One can imagine them getting caught up in the details, the molecular chaos of atomic collisions and the rotational degrees of freedom of molecules, all of which are important to the details of the thermodynamic properties of particular gases. But how would the concept of entropy have emerged from scientists staring at reams of big data describing molecular collisions? In fact, in the latter part of the nineteenth century, a genius did come along with a similar strategy, but without big data. Ludwig Boltzmann was able to derive thermodynamics from the underlying molecular chaos, and the famous hypothesis that enabled him to create this link and the entire field of statistical mechanics is worth some reflection in an essay on simplicity. As an historical note, Boltzmann was before his time. The existence of atoms was still controversial in the late nineteenth century, and his ideas met with considerable resistance. Tragically he took his own life in 1906.

Boltzmann was faced with what looked like an impossible challenge. How to make sense of the molecular chaos in a system such as a gas? His genius was to cut through the mind-boggling details and molecular complexities with a single, bold, one might say ostensibly ridiculous, statement (referring to an isolated system in equilibrium): ‘all states of the system are equally likely’. This is now called *Boltzmann’s postulate of equal a priori probabilities*. It is on page one of every book on statistical mechanics. It is an example of the null hypothesis. When in doubt, assume everything is equally likely! Boltzmann’s hypothesis logically leads to the statistical mechanical ensembles (micro-canonical, canonical and grand canonical), which form the bedrock of our modern day understanding of thermal equilibrium, and provide a richness of non-obvious predictions across physical science, which have been verified by experiment time and again. The work of many Nobel laureates in physics, celebrated for discoveries in magnetism, superconductivity, low-temperature physics, and quantum solids, are fundamentally based on Boltzmann’s postulate.

The null hypothesis is, in a sense, the ultimate antithesis of reductionism. Despite knowledge of details, the bold assertion is made that the details are irrelevant and that the observed phenomenon is a filtered outcome of an underlying random process. Such approaches are not unknown in biology, and often have an interesting existence of tolerated acceptance due to their rich predictions, despite their overt shunning of biological detail. Examples are Kimura’s theory of genetic drift [3], Hubbell’s neutral theory of biodiversity [4], and the work of Simons and co-workers on clonal expansion in stem cell differentiation [5].

In this vein, a recent work in which the author was involved provides a null model of a process as complicated as metastatic colonisation [6], and shows that randomness of cell death and proliferation, when filtered through the lens of rare events, can produce startlingly deterministic outcomes.

Scientists in all fields are struggling to adapt to ‘big data’. Have we made a rod for our own backs in harnessing information technology to record limitless details of Nature? Can one have too much information? I would say, definitely one can. But, it is not the amount of information that is really the issue, rather the fact that we risk the amount of information being inversely proportional to the ambition of the people studying it. Harking back to my discussion of thermodynamics, I doubt that Carnot *et al* would have benefitted tremendously from lists of coordinates specifying molecular collisions, and indeed such details may have hobbled their ability to discover a fundamental branch of science. But, to be sure, I do not doubt the ultimate value of big data in biology. If it is used as a resource, to test ideas and hypotheses, then it is invaluable. But the answers do not lie within the data; it is but a mirror that will reflect honestly the value of concepts brought to it.

I was recently involved in a project in which a great deal of data analysis was used to test a theory of robustness and evolvability of gene networks, which we coined Buffered Qualitative Stability [7]. The ideas were constructed through countless canteen discussions, using guiding principles of simplicity, and requiring no parameters. The resulting predictions were then rigorously tested against big data and, to our surprise and delight, verified. I was inspired by this

project, and given confidence that simplicity, in its most ascetic form, really can produce biological insights.

I have tried to challenge both physicists and biologists in making the case that biological discovery will benefit tremendously by adopting selective parts of the physics manifesto: emergence but not reductionism, and simplicity but not elegance. If we cannot find more profound and general theories of the cell, then biology may be consigned a century from now to being a telephone directory of interactions, worked out to microscopic accuracy, with little to interest our great-grand children. I for one cannot believe that the study of life deserves such a destiny. Biology is complex and the details will always be of value and often times will be of critical importance. Biology is also simple, and I hope that the arguments I have presented here encourage bold attempts at comprehensibility to be both attempted and embraced by the community.

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